PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 27 April 2000 (27.04.00)	
International application No. PCT/US99/17386	**Applicant's or agent's file reference** PENN-0693
International filing date (day/month/year) 02 August 1999 (02.08.99)	**Priority date** (day/month/year) 04 August 1998 (04.08.98)
Applicant MUZYKANTOV, Vladimir R. et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

29 February 2000 (29.02.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Kiwa Mpay
Facsimile No.: (41-22) 740.14.35	*Telephone No.: (41-22) 338.83.38*

PATENT COOPERATION TREATY

PCT

REC'D 08 DEC 2000

WIPO PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PENN-0693	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US99/17386	International filing date *(day/month/year)* 02 AUGUST 1999	Priority date *(day/month/year)* 04 AUGUST 1998
International Patent Classification (IPC) or national classification and IPC IPC(7): A61K 39/395 and US Cl.: 424/134.1, 178.1, 181.1		
Applicant THE TRUSTEES OF THE UNIVERSITY OF PENNSYLVANIA		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 4 sheets.
   - ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 0 sheets.
3. This report contains indications relating to the following items:
   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of report with regard to novelty, inventive step or industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
29 FEBRUARY 2000	03 NOVEMBER 2000
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer MARIANNE DIBRINO Telephone No. (703) 308-0196

Form PCT/IPEA/409 (cover sheet) (July 1998)*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US99/17386

I. Basis of the report

1. With regard to the **elements** of the international application:*

[X] the international application as originally filed

[X] the description:
pages 1-16 , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

[X] the claims:
pages 17-18 , as originally filed
pages NONE , as amended (together with any statement) under Article 19
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

[X] the drawings:
pages NONE , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

[X] the sequence listing part of the description:
pages NONE , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

[ ] the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

[ ] the language of publication of the international application (under Rule 48.3(b)).

[ ] the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

[ ] contained in the international application in printed form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readable form.

[ ] The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] The statement that the information recorded in computer readable form is identical to the writen sequence listing has been furnished.

4. [X] The amendments have resulted in the cancellation of:

[X] the description, pages NONE

[X] the claims, Nos. NONE

[X] the drawings, sheets/~~fig~~ NONE

5. [ ] This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

***Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US99/17386

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. statement

Novelty (N)	Claims	1-8	YES
	Claims	NONE	NO
Inventive Step (IS)	Claims	NONE	YES
	Claims	1-8	NO
Industrial Applicability (IA)	Claims	1-8	YES
	Claims	NONE	NO

2. citations and explanations (Rule 70.7)

Claims 1, 2, 5 and 6 lack an inventive step under PCT Article 33(3) as being obvious over Bowes et al (Neurology, 1995) in view of Imaizumi and further in view of Mulligan et al and Panes et al. Bowes et al teach that administration of an anti-ICAM-1 mAb and the drug tPA to rabbits prevents leukocyte adhesion and increases post ischemic duration at which thrombolytic therapy remains effective in cerebral ischemia and reperfusion (especially Abstract). Bowes et al also teach that administration of tPA alone improves neurologic outcome in models of ischemia, but that obstacles exist to therapy, and further that reperfusion may also result in additional neurologic damage as ischemic tissue is reoxygenated. Bowes et al do not teach a method for targeting and prolonging association of a selected drug to the luminal surface of pulmonary vascular endothelium comprising administering to an animal a selected drug in combination with a non-internalizable antibody which binds to the luminal surface of the endothelium. Imaizumi teaches a method of administration of mouse anti-rat mAb 1A29 (anti-ICAM-1)inhibits ICAM-1 on pulmonary vascular endothelial cells and impairs damage due to reperfusion injury. Imaizumi teaches that impairment of reperfusion injury is closely associated with vascular endothelial cell damage by neutrophils. Imaizumi further teaches that in flowing blood, neutrophils do not adhere to vascular endothelial cells in the normal state; adhesion of neutrophils to vascular endothelial cells is necessary to induce vascular endothelial cell damage after ischemia and reperfusion, and an increase in the expression of adhesion molecule (especially page 1853, column 1). Imaizumi teaches an increase in the expression of adhesion molecules in vascular endothelial cells activated by reperfusion and a resultant increase in the binding to neutrophils. Mulligan et al teach anti-ICAM-1 mAb 1A29 accumulates in the pulmonary vasculature, i.e., binds to the luminal surface of the endothelium and is not internalized, challenged with pro-inflammatory agents, and that blocking of ICAM-1 is tissue protective in a manner in which neutrophil recruitment is attenuated. Panes et al teach that ICAM-1 is consitutively expressed on vascular endothelium of the rat and there are significant regional differences in magnitude of expression. It (Continued on Supplemental Sheet.)

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

V. 2. REASONED STATEMENTS - CITATIONS AND EXPLANATIONS (Continued):
would have been prima facie obvious at the time the invention was made to have substituted the mAb 1A29 of Imaizumi or of Mulligan et al for the anti-ICAM-1 mAb in the composition of Bowes et al and to have used the combined composition in the method of Imaizumi. One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to treat ischemia and pulmonary reperfusion injury in rats.

Applicant's response to the Written Opinion has been fully considered but is not deemed persuasive. Applicant's objections are that Bowes et al do not teach that the combination of an anti-ICAM-1 antibody in conjunction with tPA did not work better than each compound alone in reducing neurological damage and that Imaizumi does not teach or suggest that the 1A29 antibody itself had any effects of its own to inhibit adhesion on endothelial cells. However, Bowes et al teach (Abstract) "...the combination of a[anti]-ICAM-1...and tPA...significantly improved neurologic outcome even though neither substance was effective alone...", and Imaizumi et al teach (on page 1853, the paragraph bridging columns 1 and 2) "...1A29 used in this study are neutralizing antibodies that specifically inhibit...ICAM-1 on vascular endothelial cells...".

Claims 3, 4, 7 and 8 lack an inventive step under PCT Article 33(3) as being obvious over the prior art as applied in the immediately preceding paragraph and further in view of Torchilin et al, Muzykantov et al (BBA, 1986) and Muzykantov et al (Amer J Physiol, 1996). The reference teachings differ from the instant claims in that they do not teach conjugation of the selected drug to the antibody either before or after administration by chemical modification. Runge et al (PNAS, 1987) teach the thrombolytic drug tPA can be efficiently directed to the site of a thrombus by conjugation to an anti-fibrin monoclonal antibody, resulting in both more potent and more selective thrombolysis (especially Abstract). Torchilin et al teach that targeted accumulation of thrombolytic enzymes in the region of thrombus location can be achieved by their coimmobilization with specific antibodies (especially Abstract). Torchilin et al further teach drawbacks in administration of tPA alone include necessity of prolonged and continuous administration due to rapid physiologic inactivation far from the site of thrombolysis (especially page 322) may be resolved by the use of antibody-immobilized tPA. Muzykantov et al (BBA, 1986) teach targeting of fibrinolytic agents using antibody to regions of the vascular bed having an increased probability of clot formation. Muzykantov et al (Amer J Physiol, 1996) teach targeting of drugs to the pulmonary vascular endothelium using antibody. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have administered a thrombolytic enzyme drug such as tPA conjugated to an anti-ICAM-1 mAb such as the 1A29 mAb either directly or indirectly by chemical modification of the tPA. One of ordinary skill in the art at the time the invention was made would have been motivated to do this to effectively target tPA as taught by Torchilin et al and Muzykantov et al and to prevent the deleterious side effects of administering tPA alone as taught by Torchilin et al or to more effectively target the tPA to regions of the vascular bed having an increased probability of clot formation as taught by Muzykantov et al. The skilled artisan at the time the invention was made was aware of methods and reagents for indirectly coupling proteins, such as the streptavidin-biotin system.

Claims 1-8 meet the criteria of PCT Article 33(4) because the claimed method is useful in drug targeting.

Applicant's response to the Written Opinion has been fully considered but is not deemed persuasive. Applicant's objections are that Bowes et al do not teach that the combination of an anti-ICAM-1 antibody in conjunction with tPA did not work better than each compound alone in reducing neurological damage and that Imaizumi does not teach or suggest that the 1A29 antibody itself had any effects of its own to inhibit adhesion on endothelial cells. However, Bowes et al teach (Abstract) "...the combination of a[anti]-ICAM-1...and tPA...significantly improved neurologic outcome even though neither substance was effective alone...", and Imaizumi et al teach (on page 1853, the paragraph bridging columns 1 and 2) "...1A29 used in this study are neutralizing antibodies that specifically inhibit...ICAM-1 on vascular endothelial cells...". The remainder of the references are argued individually by the Applicant. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the objections are based on combinations of references.

---------- NEW CITATIONS ----------
NONE

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To: JANE MASSEY LICATA
LAW OFFICES OF JANE MASSEY LICATA
66 E. MAIN STREET
MARLTON, NEW JERSEY 08053

Docket System ✓
Status Report ✓
Docket Book ✓
9/16/00 ANS

PCT

WRITTEN OPINION

(PCT Rule 66)

Date of Mailing *(day/month/year)*	16 AUG 2000
Applicant's or agent's file reference: PENN-0693	REPLY DUE within ONE months from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US99/17386	02 AUGUST 1999	04 AUGUST 1998

International Patent Classification (IPC) or both national classification and IPC
IPC(7): A61K 39/395 and US Cl.: 424/134.1, 178.1, 181.1

Applicant
THE TRUSTEES OF THE UNIVERSITY OF PENNSYLVANIA

1. This written opinion is the first (first, etc.) drawn by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

- I [X] Basis of the opinion
- II [ ] Priority
- III [ ] Non-establishment of opinion with regard to novelty, inventive step or industrial applicability
- IV [ ] Lack of unity of invention
- V [X] Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI [ ] Certain documents cited
- VII [ ] Certain defects in the international application
- VIII [ ] Certain observations on the international application

3. The applicant is hereby invited to reply to this opinion.

When? See the time limit indicated above. ~~The applicant may, before the expiration of that time limit, request this Authority to grant an extension., see Rule 66.2(d).~~

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 *bis*.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 04 DECEMBER 2000

Name and mailing address of the IPEA/US	Authorized officer
Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	MARIANNE DIBRINO
Facsimile No. (703) 305-3230	Telephone No. (703) 308-0196

Form PCT/IPEA/408 (cover sheet) (July 1998)★

WRITTEN OPINION

International application No.
PCT/US99/17386

I. Basis of the opinion

1. With regard to the **elements** of the international application:*

[X] the international application as originally filed

[X] the description:
pages 1-16 , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

[X] the claims:
pages 17-18 , as originally filed
pages NONE , as amended (together with any statement) under Article 19
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

[X] the drawings:
pages NONE , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

[X] the sequence listing part of the description:
pages NONE , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

[ ] the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

[ ] the language of publication of the international application (under Rule 48.3(b)).

[ ] the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the written opinion was drawn on the basis of the sequence listing:

[ ] contained in the international application in printed form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readable form.

[ ] The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

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4. [X] The amendments have resulted in the cancellation of:

[X] the description, pages NONE

[X] the claims, Nos. NONE

[X] the drawings, sheets/~~fig~~ NONE

5. [ ] This opinion has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed".*

WRITTEN OPINION

International application No.
PCT/US99/17386

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. statement

Novelty (N)	Claims	1-8	YES
	Claims	NONE	NO
Inventive Step (IS)	Claims	NONE	YES
	Claims	1-8	NO
Industrial Applicability (IA)	Claims	1-8	YES
	Claims	NONE	NO

2. citations and explanations

Claims 1, 2, 5 and 6 lack an inventive step under PCT Article 33(3) as being obvious over Bowes et al (Neurology, 1995) in view of Imaizumi and further in view of Mulligan et al and Panes et al. Bowes et al teach that administration of an anti-ICAM-1 mAb and the drug tPA to rabbits prevents leukocyte adhesion and increases post ischemic duration at which thrombolytic therapy remains effective in cerebral ischemia and reperfusion (especially Abstract). Bowes et al also teach that administration of tPA alone improves neurologic outcome in models of ischemia, but that obstacles exist to therapy, and further that reperfusion may also result in additional neurologic damage as ischemic tissue is reoxygenated. Bowes et al do not teach a method for targeting and prolonging association of a selected drug to the luminal surface of pulmonary vascular endothelium comprising administering to an animal a selected drug in combination with a non-internalizable antibody which binds to the luminal surface of the endothelium. Imaizumi teaches a method of administration of mouse anti-rat mAb 1A29 (anti-ICAM-1)inhibits ICAM-1 on pulmonary vascular endothelial cells and impairs damage due to reperfusion injury. Imaizumi teaches that impairment of reperfusion injury is closely associated with vascular endothelial cell damage by neutrophils. Imaizumi further teaches that in flowing blood, neutrophils do not adhere to vascular endothelial cells in the normal state; adhesion of neutrophils to vascular endothelial cells is necessary to induce vascular endothelial cell damage after ischemia and reperfusion, and an increase in the expression of adhesion molecule (especially page 1853, column 1). Imaizumi teaches an increase in the expression of adhesion molecules in vascular endothelial cells activated by reperfusion and a resultant increase in the binding to neutrophils. Mulligan et al teach anti-ICAM-1 mAb 1A29 accumulates in the pulmonary vasculature, i.e., binds to the luminal surface of the endothelium and is not internalized, challenged with pro-inflammatory agents, and that blocking of ICAM-1 is tissue protective in a manner in which neutrophil recruitment is attenuated. Panes et al teach that ICAM-1 is consitutively (Continued on Supplemental Sheet.)

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

TIME LIMIT:

The time limit set for response to a Written Opinion may not be extended. 37 CFR 1.484(d). Any response received after the expiration of the time limit set in the Written Opinion will not be considered in preparing the International Preliminary Examination Report.

V. 2. REASONED STATEMENTS - CITATIONS AND EXPLANATIONS (Continued):
expressed on vascular endothelium of the rat and there are significant regional differences in magnitude of expression. It would have been prima facie obvious at the time the invention was made to have substituted the mAb 1A29 of Imaizumi or of Mulligan et al for the anti-ICAM-1 mAb in the composition of Bowes et al and to have used the combined composition in the method of Imaizumi. One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to treat ischemia and pulmonary reperfusion injury in rats.

Claims 3, 4, 7 and 8 lack an inventive step under PCT Article 33(3) as being obvious over the prior art as applied in the immediately preceding paragraph and further in view of Torchilin et al, Muzykantov et al (BBA, 1986) and Muzykantov et al (Amer J Physiol, 1996). The reference teachings differ from the instant claims in that they do not teach conjugation of the selected drug to the antibody either before or after administration by chemical modification. Runge et al (PNAS, 1987) teach the thrombolytic drug tPA can be efficiently directed to the site of a thrombus by conjugation to an anti-fibrin monoclonal antibody, resulting in both more potent and more selective thrombolysis (especially Abstract). Torchilin et al teach that targeted accumulation of thrombolytic enzymes in the region of thrombus location can be achieved by their coimmobilization with specific antibodies (especially Abstract). Torchilin et al further teach drawbacks in administration of tPA alone include necessity of prolonged and continuous administration due to rapid physiologic inactivation far from the site of thrombolysis (especially page 322) may be resolved by the use of antibody-immobilized tPA. Muzykantov et al (BBA, 1986) teach targeting of fibrinolytic agents using antibody to regions of the vascular bed having an increased probability of clot formation. Muzykantov et al (Amer J Physiol, 1996) teach targeting of drugs to the pulmonary vascular endothelium using antibody. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have administered a thrombolytic enzyme drug such as tPA conjugated to an anti-ICAM-1 mAb such as the 1A29 mAb either directly or indirectly by chemical modification of the tPA. One of ordinary skill in the art at the time the invention was made would have been motivated to do this to effectively target tPA as taught by Torchilin et al and Muzykantov et al and to prevent the deleterious side effects of administering tPA alone as taught by Torchilin et al or to more effectively target the tPA to regions of the vascular bed having an increased probability of clot formation as taught by Muzykantov et al. The skilled artisan at the time the invention was made was aware of methods and reagents for indirectly coupling proteins, such as the streptavidin-biotin system.

Claims 1-8 meet the criteria of PCT Article 33(4) because the claimed method is useful in drug targeting.

---------- NEW CITATIONS ----------
NONE

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To: JANE MASSEY LICATA
LAW OFFICES OF JANE MASSEY LICATA
66 E. MAIN STREET
MARLTON, NEW JERSEY 08053

Docket System ✓
Status ✓
Docket Book ✓

NP = 2-401

PCT

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of Mailing *(day/month/year)*	05 DEC 2000
Applicant's or agent's file reference: PENN-0693	IMPORTANT NOTIFICATION

International application No.	International filing date *(day/month/year)*	Priority Date *(day/month/year)*
PCT/US99/17386	02 AUGUST 1999	04 AUGUST 1998

Applicant
THE TRUSTEES OF THE UNIVERSITY OF PENNSYLVANIA

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/US	Authorized officer
Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	MARIANNE DIBRINO
Facsimile No. (703) 305-3230	Telephone No. (703) 308-0196

Form PCT/IPEA/416 (July 1992)★

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PENN-0693	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US99/17386	International filing date *(day/month/year)* 02 AUGUST 1999	Priority date *(day/month/year)* 04 AUGUST 1998
International Patent Classification (IPC) or national classification and IPC IPC(7): A61K 39/395 and US Cl.: 424/134.1, 178.1, 181.1		
Applicant THE TRUSTEES OF THE UNIVERSITY OF PENNSYLVANIA		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

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3. This report contains indications relating to the following items:

   I ☒ Basis of the report

   II ☐ Priority

   III ☐ Non-establishment of report with regard to novelty, inventive step or industrial applicability

   IV ☐ Lack of unity of invention

   V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

   VI ☐ Certain documents cited

   VII ☐ Certain defects in the international application

   VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
29 FEBRUARY 2000	03 NOVEMBER 2000
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer MARIANNE DIBRINO Telephone No. (703) 308-0196

Form PCT/IPEA/409 (cover sheet) (July 1998)★

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US99/17386

I. Basis of the report

1. With regard to the **elements** of the international application:*

[X] the international application as originally filed

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pages 1-16 , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

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pages NONE , as originally filed
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These elements were available or furnished to this Authority in the following language _____ which is:

[ ] the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

[ ] the language of publication of the international application (under Rule 48.3(b)).

[ ] the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

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4. [X] The amendments have resulted in the cancellation of:

[X] the description, pages NONE

[X] the claims, Nos. NONE

[X] the drawings, sheets/~~fig~~ NONE

5. [ ] This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

***Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US99/17386

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. statement

Novelty (N)	Claims	1-8	YES
	Claims	NONE	NO
Inventive Step (IS)	Claims	NONE	YES
	Claims	1-8	NO
Industrial Applicability (IA)	Claims	1-8	YES
	Claims	NONE	NO

2. citations and explanations (Rule 70.7)

Claims 1, 2, 5 and 6 lack an inventive step under PCT Article 33(3) as being obvious over Bowes et al (Neurology, 1995) in view of Imaizumi and further in view of Mulligan et al and Panes et al. Bowes et al teach that administration of an anti-ICAM-1 mAb and the drug tPA to rabbits prevents leukocyte adhesion and increases post ischemic duration at which thrombolytic therapy remains effective in cerebral ischemia and reperfusion (especially Abstract). Bowes et al also teach that administration of tPA alone improves neurologic outcome in models of ischemia, but that obstacles exist to therapy, and further that reperfusion may also result in additional neurologic damage as ischemic tissue is reoxygenated. Bowes et al do not teach a method for targeting and prolonging association of a selected drug to the luminal surface of pulmonary vascular endothelium comprising administering to an animal a selected drug in combination with a non-internalizable antibody which binds to the luminal surface of the endothelium. Imaizumi teaches a method of administration of mouse anti-rat mAb 1A29 (anti-ICAM-1)inhibits ICAM-1 on pulmonary vascular endothelial cells and impairs damage due to reperfusion injury. Imaizumi teaches that impairment of reperfusion injury is closely associated with vascular endothelial cell damage by neutrophils. Imaizumi further teaches that in flowing blood, neutrophils do not adhere to vascular endothelial cells in the normal state; adhesion of neutrophils to vascular endothelial cells is necessary to induce vascular endothelial cell damage after ischemia and reperfusion, and an increase in the expression of adhesion molecule (especially page 1853, column 1). Imaizumi teaches an increase in the expression of adhesion molecules in vascular endothelial cells activated by reperfusion and a resultant increase in the binding to neutrophils. Mulligan et al teach anti-ICAM-1 mAb 1A29 accumulates in the pulmonary vasculature, i.e., binds to the luminal surface of the endothelium and is not internalized, challenged with pro-inflammatory agents, and that blocking of ICAM-1 is tissue protective in a manner in which neutrophil recruitment is attenuated. Panes et al teach that ICAM-1 is consitutively expressed on vascular endothelium of the rat and there are significant regional differences in magnitude of expression. It (Continued on Supplemental Sheet.)

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

V. 2. REASONED STATEMENTS - CITATIONS AND EXPLANATIONS (Continued):
would have been prima facie obvious at the time the invention was made to have substituted the mAb 1A29 of Imaizumi or of Mulligan et al for the anti-ICAM-1 mAb in the composition of Bowes et al and to have used the combined composition in the method of Imaizumi. One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to treat ischemia and pulmonary reperfusion injury in rats.

Applicant's response to the Written Opinion has been fully considered but is not deemed persuasive. Applicant's objections are that Bowes et al do not teach that the combination of an anti-ICAM-1 antibody in conjunction with tPA did not work better than each compound alone in reducing neurological damage and that Imaizumi does not teach or suggest that the 1A29 antibody itself had any effects of its own to inhibit adhesion on endothelial cells. However, Bowes et al teach (Abstract) "...the combination of a[anti]-ICAM-1...and tPA...significantly improved neurologic outcome even though neither substance was effective alone...", and Imaizumi et al teach (on page 1853, the paragraph bridging columns 1 and 2) "...1A29 used in this study are neutralizing antibodies that specifically inhibit...ICAM-1 on vascular endothelial cells...".

Claims 3, 4, 7 and 8 lack an inventive step under PCT Article 33(3) as being obvious over the prior art as applied in the immediately preceding paragraph and further in view of Torchilin et al, Muzykantov et al (BBA, 1986) and Muzykantov et al (Amer J Physiol, 1996). The reference teachings differ from the instant claims in that they do not teach conjugation of the selected drug to the antibody either before or after administration by chemical modification. Runge et al (PNAS, 1987) teach the thrombolytic drug tPA can be efficiently directed to the site of a thrombus by conjugation to an anti-fibrin monoclonal antibody, resulting in both more potent and more selective thrombolysis (especially Abstract). Torchilin et al teach that targeted accumulation of thrombolytic enzymes in the region of thrombus location can be achieved by their coimmobilization with specific antibodies (especially Abstract). Torchilin et al further teach drawbacks in administration of tPA alone include necessity of prolonged and continuous administration due to rapid physiologic inactivation far from the site of thrombolysis (especially page 322) may be resolved by the use of antibody-immobilized tPA. Muzykantov et al (BBA, 1986) teach targeting of fibrinolytic agents using antibody to regions of the vascular bed having an increased probability of clot formation. Muzykantov et al (Amer J Physiol, 1996) teach targeting of drugs to the pulmonary vascular endothelium using antibody. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have administered a thrombolytic enzyme drug such as tPA conjugated to an anti-ICAM-1 mAb such as the 1A29 mAb either directly or indirectly by chemical modification of the tPA. One of ordinary skill in the art at the time the invention was made would have been motivated to do this to effectively target tPA as taught by Torchilin et al and Muzykantov et al and to prevent the deleterious side effects of administering tPA alone as taught by Torchilin et al or to more effectively target the tPA to regions of the vascular bed having an increased probability of clot formation as taught by Muzykantov et al. The skilled artisan at the time the invention was made was aware of methods and reagents for indirectly coupling proteins, such as the streptavidin-biotin system.

Claims 1-8 meet the criteria of PCT Article 33(4) because the claimed method is useful in drug targeting.

Applicant's response to the Written Opinion has been fully considered but is not deemed persuasive. Applicant's objections are that Bowes et al do not teach that the combination of an anti-ICAM-1 antibody in conjunction with tPA did not work better than each compound alone in reducing neurological damage and that Imaizumi does not teach or suggest that the 1A29 antibody itself had any effects of its own to inhibit adhesion on endothelial cells. However, Bowes et al teach (Abstract) "...the combination of a[anti]-ICAM-1...and tPA...significantly improved neurologic outcome even though neither substance was effective alone...", and Imaizumi et al teach (on page 1853, the paragraph bridging columns 1 and 2) "...1A29 used in this study are neutralizing antibodies that specifically inhibit...ICAM-1 on vascular endothelial cells...". The remainder of the references are argued individually by the Applicant. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the objections are based on combinations of references.

---------- NEW CITATIONS ----------
NONE

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/17386

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :A61K 39/395
US CL :424/134.1, 178.1, 181.1
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/134.1, 178.1, 181.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Please See Extra Sheet.

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	PANES et al. Regional differences in constitutive and induced ICAM-1 expression in vivo. Amer. J. Physiol. 1995, Vol. 269, pages H1955-H1964, see entire document.	1-8
Y	RUNGE et al. Antibody-enhanced thrombolysis: Targeting of tissue plasminogen activator in vivo. Proc. Natl. Acad. Sci. USA. November 1987, Vol. 84, pages 7659-7662, see entire document.	1-8
Y	IMAIZUMI, T. Effect of Antibodies Against Neutrophil and Endothelial Adhesion Molecules on Reperfusion Injury After Pulmonary Ischemia. Transpl. Proc. August 1994, Vol. 26, No. 4, pages 1851-1854, see entire document.	1-8

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 22 OCTOBER 1999	Date of mailing of the international search report 23 DEC 1999
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer MARIANNE DIBRINO Telephone No. (703) 308-0196

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/17386

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	MULLIGAN et al. Tumor Necrosis Factor α Regulates in Vivo Intrapulmonary Expression of ICAM-1. Amer. J. Pathol. June 1993, Vol. 142, No. 6, pages 1739-1749, see entire article.	1-8
Y	MUZYKANTOV et al. Immunotargeting of erythrocyte-bound streptokinase provides local lysis of a fibrin clot. Biochim. Biophys. Acta. 1986, Vol. 884, pages 355-362, see entire article.	1-8
Y	TORCHILIN et al. Long acting thrombolytic immobilized enzymes. J. Contr. Rel. 1985, Vol. 2, pages 321-330, see entire article.	1-8
Y	MUZYKANTOV et al. Endothelial cells internalize monoclonal antibody to angiotensin-converting enzyme. Amer. J. Physiol. 1996, Vol. 270, pages L704-713, see entire article.	1-8
Y	RUNGE et al. Conjugation to an Antifibrin Monoclonal Antibody Enhances the Fibrinolytic Potency of Tissue Plasminogen Activator in Vitro. Biochem. 1988, Vol. 27, pages 1153-1157, see entire article.	1-8
Y	BOWES et al. Monoclonal Antibody to the ICAM-1 Adhesion Site Reduces Neurological Damage in a Rabbit Cerebral Embolism Stroke Model. Exp. Neurology. 1993, Vol. 119, pages 215-219, especially page 216, column 1 and page 218, Summary.	1-8
Y	BOWES et al. Monoclonal antibodies preventing leukocyte activation reduce experimental neurologic injury and enhance efficacy of thrombolytic therapy. Neurology. April 1995, Vol. 45, pages 815-819, see entire article.	1-8

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/17386

B. FIELDS SEARCHED
Documentation other than minimum documentation that are included in the fields searched:

STN (Biosis, Medline, Embase, Caplus), WEST
search terms: Murciano, Juan Carlos, Granger, D. Neil, ICAM, mab 1A29, tPA, streptokinse, anticoagulant, non-inemalizable, antibody, pulmonary, thrombolysis, clot, pulmonary reperfusion

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/17386

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"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
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Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/17386

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/17386

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search terms: Murciano, Juan Carlos, Granger, D. Neil, ICAM, mab 1A29, tPA, streptokinse, anticoagulant, non-inernalizable, antibody, pulmonary, thrombolysis, clot, pulmonary reperfusion

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
Before the United States International
Preliminary Examining Authority
for the Patent Cooperation Treaty

Applicant: **The Trustees of the University of Pennsylvania et al.**

International Application No.: **PCT/US99/17386**

International Filing Date: **02 August 1999**

Attorney Ref.: **PENN-0693**

Assistant Commissioner of Patents
Box PCT
Washington, D.C. 20231

"Express Mail" Label No. EL603802625US
Date of Deposit - September 14, 2000

I hereby certify that this paper is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to the Assistnt Commissioner of Patents, Washington, Box PCT, D.C. 20231.

By Suzanne Sparkman
Typed Name: **Suzanne Sparkman**

Dear Sir:

Response to Written Opinion

This is in response to the Written Opinion mailed 16 August 2000.

Claims 1, 2, 5 and 6 have been rejected for lacking an inventive step under PCT Article 33(3) as being obvious over Bowes et al. (1995) in view of Imaizumi (1994) and further in view of Mulligan et al. (1993) and Panes et al. (1995). The Examiner suggests that it would have been prima facie obvious for one of skill to have substituted the mAb 1A29 of Imaizumi or of Mulligan et al. for the anti-ICAM-1 mAb in the composition of Bowes et al., and then to have used the combined composition in the method of Imaizumi to treat ischemia and pulmonary reperfusion injury in rats. Applicants respectfully disagree.

Bowes et al. (1995) teach use of a anti-ICAM-1 antibody in conjunction with tPA in an animal model of cerebral embolism stroke for study of the thrombolytic effects of tPA both alone and in the presence of the antibody. The results showed that the combination of the two did not work better than each compound alone in reducing neurological damage. Nowhere does this paper teach or suggest targeting the luminal surface of pulmonary vascular endothelium with a drug in combination with a non-internalizable antibody.

The secondary references fail to overcome the deficiencies in the teachings of Bowes et al.

Imaizumi (1994) discloses use of an antibody to ICAM-1, 1A29, significantly enhanced the inhibitory effect of an anti-adhesion molecule antibody, WT.1, on adhesion of neutrophils to vascular endothelial cells. Nowhere does this paper teach or suggest that the 1A29 antibody itself had any effects of its own to inhibit adhesion on endothelial cells. Further, nowhere does this paper teach or suggest targeting the luminal surface of pulmonary vascular endothelium with a drug in combination with a non-internalizable antibody.

Panes et al. (1995) disclose that the 1A29 anti-ICAM-1 antibody reacts with normal endothelial cells in the rat vasculature and that injection of TNF or endotoxin stimulates endothelial binding of this antibody. Nowhere, however, does this paper teach or suggest targeting the luminal surface of pulmonary vascular endothelium with a drug in combination with a non-internalizable antibody.

Mulligan et al. (1993) teaches that radiolabelled mAb 1A29 accumulates in the vasculature challenged with pro-inflammatory agents such as TNF and endotoxin. However, nowhere does this paper teach or suggest targeting the luminal surface of pulmonary vascular endothelium with a drug in combination with a non-internalizable antibody.

Therefore, this combination of prior art fails to teach the limitations of the claims as filed which recite administration of a drug in combination with a non-internalizable antibody which binds to an antigen on the luminal surface of the pulmonary vascular endothelium. Therefore, this combination of prior art cannot render the instant invention obvious.

Claims 3, 4, 7 and 8 have been rejected for lacking an inventive step under PCT Article 33(3) as being obvious over the prior art as applied above and further in view of Torchilin et al., Muzykantov et al. (1986) and Muzykantov et al. (1996). The Examiner suggests that it would have been prima facie obvious to have administered a thrombolytic drug such as tPA conjugated to an anti-ICAM-1 mAb such as 1A29 either directly or indirectly by chemical modification of the tPA. The Examiner further suggests the motivation is provided by the teachings of Torchilin et al., and Muzykantov et al., both of which teach that targeting. Applicants respectfully disagree.

As discussed supra, the teachings of Bowes et al., Panes et al., Imaizumi, and Mulligan et al. fail to teach administration of a drug in combination with a non-internalizable antibody which binds to an antigen on the luminal surface of the pulmonary vascular endothelium. The additional prior art fails to overcome these deficiencies in teachings.

Torchilin and Mazeav (1985) teaches that enzymes such as tPA can be made more effective by administration in slow release preparations as well as by modifying the enzyme with a compound that has the ability to bind to the target. There is a general discussion of using antibodies as one such modification tool. However, nowhere does this prior art reference teach or suggest administration of a drug in

combination with a non-internalizable antibody which binds to an antigen on the luminal surface of the pulmonary vascular endothelium.

Muzykantov et al. (1986) discloses an anti-collagen antibody-erythrocyte-streptokinase complex that is formed using an avidin-biotin interaction. This complex provided for local lysis of fibrin clots. However, nowhere does this paper teach or suggest administration of a drug in combination with a non-internalizable antibody which binds to an antigen on the luminal surface of the pulmonary vascular endothelium.

Muzykantov et al. (1996) teaches that endothelial cells internalize antibodies against angiotensin-converting enzyme which provided for a useful method of targeting genes by intracellular delivery of the agent conjugated to such an antibody. This paper does not teach administration of a drug in combination with a non-internalizable antibody which binds to an antigen on the luminal surface of the pulmonary vascular endothelium.

The Examiner has also mentioned an article by Runge et al. (1987) which the Examiner suggests teaches that tPA can be efficiently directed to the site of a thrombus by conjugation to an anti-fibrin mAb, resulting in a more potent and selective thrombin. However, careful review of this paper reveals that this paper fails to teach or suggest administration of a drug in combination with a non-internalizable antibody which binds to an antigen on the luminal surface of the pulmonary vascular endothelium.

Accordingly, this combination of prior art fails to teach the limitations of the claims of the instant invention and,

therefore, cannot make the instant invention obvious.

Respectfully submitted,

Jane Massey Licata
Registration No. 32,257

Date: 14 September 2000

Law Offices of Jane Massey Licata
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(856) 810-1515